UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/091,578	10/06/98	MADISON E	19191.0002

HM12/0815

DAVID G PERRYMAN
NEEDLE & ROSENBERG
127 PEACHTREE STREET N E
SUITE 1200 THE CANDLER BUILDING
ATLANTA GA 30303-1811

EXAMINER	
DIBRINO, M	
ART UNIT	**PAPER NUMBER**
1644	15

DATE MAILED: 08/15/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/091,578	Madison et al
Examiner	**Group Art Unit**
Marianne DiBrino	1644

☒ Responsive to communication(s) filed on *May 15, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1 and 3-65* is/are pending in the applicat

Of the above, claim(s) *25-64* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 3-24, and 65* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Applicant's amendment filed 5/15/00 is acknowledged and has been entered.

Claims 1, 3-24 and 65 are presently being examined.

2. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: (1) the declaration lists the filing date as 6/19/98, whereas the filing date of the instant application is 10/6/98; (2) the declaration states that filing was with amendments through November 17, 1998, whereas the filing date of the preliminary amendment is November 24, 1998; (3) the declaration is defective in claiming priority to PCT/US96/20577 under 35 U.S.C. 119a-d. Priority claim should be made under 35 U.S.C. 120.

3. Upon reconsideration of the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999; the following rejection is set forth herein.

4. Claims 1 and 4-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed CD1-blocking agent which is LAM.

The instant claims encompass an agent comprising an isolated peptide mimetic. There is insufficient disclosure in the specification on such a an agent comprising an isolated peptide mimetic. A peptide mimetic is disclosed in the instant specification on page 12 at lines 7-9 to "include a chemical compound, or an organic molecule or any other peptide mimetic, the structure of which is based on or derived from a binding region of a protein." There are insufficient relevant identifying structural characteristics disclosed by the instant specification for which chemical compounds or are organic molecules other than proteins or peptides are

peptide mimetics that bind a selected target.

The following are new grounds of rejection necessitated by the amendment filed 5/15/00.

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1, 3-13, 15-16 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Paoni et al (Protein Eng., Vol. 6, 1993, pages 529-534, provided in the last office action) as evidenced by Gething et al (EMBO Journal, Vol. 7, 1988, pages 2731-2740, provided in the last office action).

Paoni et al teach a targeted therapeutic agent comprising a therapeutic functional entity (tPA) linked to an optimized surface loop (amino acid residues EIHPV of vampire bat tPA) that binds a selected target (fibrin) (especially page 533, column 1, last paragraph, and column 2). Paoni et al teach that the entity is loop-grafted tPA (especially page 533, column 1, last paragraph, and column 2). Claim 4 is included because the term "medical or diagnostic device" encompasses tPA, which can function in thrombolysis (especially page 533, last sentence and Introduction section, page 529). Claim 8 is included because tPA is an enzyme as evidenced by Gething et al (especially first sentence of Introduction section on page 2731). For the purpose of examination, claims are given their broadest reasonable interpretation. A peptide mimetic is disclosed in the instant specification on page 12 at lines 7-9 to "include a chemical compound, or an organic molecule or any other peptide mimetic, the structure of which is based on or derived from a binding region of a protein." A definition for the term "grafted" is not disclosed in the instant specification. Instant claim 3 is included because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims, i.e., as in "and is optimized prior to grafting."

The reference teachings anticipate the claimed invention.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims

was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1 and 3-24 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bode et al (Circulation, Vol. 84, 1991, pages 805-813, made of recored in the previous office action) in view of Smith et al (J. Biol. Chem. Vol. 269, No. 52, pages 32788-32795, 1994) and further in view of Barbas et al (Proc. Natl. Acad. Sci. Vol. 90, 1993, pages 10003-10007, made of recored in the previous office action), Todd et al (Clinical Diagnosis and Management by Laboratory Methods, 1979, Vol. 1, page 252, made of recored in the previous office action) and Johannessen et al (Thrombosis and Haemostasis, Vol. 63, 1990, pages 54-59, made of recored in the previous office action).

Bode et al teach a targeted therapeutic agent comprising a therapeutic functional entity (urokinase, a plasminogen activator) linked to a protein comprising an antibody (7E3, specific for platelet membrane glycoprotein IIb/IIIa) (especially Abstract and page 805). Bode et al also teach that arterial thrombi contain a high concentration of activated platelets, that platelets play a key role when initially reperfused vessels reocclude, and that combined administration of 7E3 and a thrombolytic agent reduces the rate of reocclusion and enhances the speed and efficacy of reperfusion in experimental animals (especially page 805, paragraph 1).

Bode et al do not teach that the therapeutic functional entity is linked to a protein which has undergone protein loop grafting, the nonendogenous loop binding a specific target. Bode et al do not teach that the therapeutic functional entity is linked to an optimized, high affinity polyamino acid that specifically binds a selected target that is $\alpha_v\beta_3$ or $\alpha II_b\beta_3$, integrins that bind an RGD motif.

Smith et al teach a monoclonal antibodies which were derived from mAb Fab-9 using an antibody engineering strategy that was employed to build high affinity ligands of one or both of the integrins $\alpha_v\beta_3$ or $\alpha II_b\beta_3$, specifically by subjecting mAb Fab-9 to a motif optimization (especially Abstract), i.e., affinity maturation. Smith et al also teach one such antibody MTF-10 that has a 70-fold higher affinity for $\alpha II_b\beta_3$ than for $\alpha_v\beta_3$. Smith et al further teach the usefulness of said antibodies in blocking host immune responses to the said integrins which have been implicated in numerous diseases. Smith et al teach that an antagonist of the platelet integrin $\alpha II_b\beta_3$ would arrest platelet aggregation and could find wide application in treating thrombotic episodes and blocking platelet function in vivo (especially page 32795, column 1, last paragraph).

Barbas et al teach Fab-9, an isolated, optimized, high-affinity polyamino acid (the complementarity determining region, HCDR3, of antibody molecule Fab-9 optimized with an

RGD sequence) that specifically binds a selected target (an integrin that binds to an RGD motif, $\alpha_{IIb}\beta_3$ or $\alpha_v\beta_3$ (especially Figure 1 legend and Abstract). Barbas et al teach that integrin $\alpha_{IIb}\beta_3$ exacerbated an artherosclerotic lesion by enabling platelet adhesion and thrombus formation at the existing atherosclerotic plaque (especially page 10003, , column 2, lines 3-6) and teach design of anti-receptor antibodies, specifically for $\alpha_{IIb}\beta_3$ or $\alpha_v\beta_3$ by protein loop grafting of RGD (especially page 10004).

Todd et al teach that "plasminogen is the circulating proenzyme from which the fibrinolytic molecule, plasmin, is derived. The inactive protein can be converted to the enzymatically effective form by several endogenous activators found in many tissues, particularly within the vascular wall, and in the urinary tract, where the activator is specifically referred to as urokinase" (especially page 252, column 2, lines 1-9 of section entitled "Physiology").

Johannessen et al teach that tissue type plasminogen activator (t-PA) has a high thrombolytic efficacy due to its high affinity for fibrin which results in a binding induced increase in activity as well as localization of the fibrinolytic activity to the site of the clot. Johannessen et al teach that fibrinolytic activity associated with t-PA is accompanied by only modest systemic activation of plasmin and limited degradation of plasma fibrinogen, and the desirability of producing an analogue with a long half-life in the circulation given the fact that t-PA is rapidly cleared from the bloodstream (especially Introduction section).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted the 7E3 antibody in the invention of Bode et al with another high affinity monoclonal antibody specific for a platelet integrin, particularly one such as the MTF-10 antibody of Smith et al. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to provide an antibody with high affinity to an integrin which is present on platelets and with lower affinity to integrins on other cell types. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have substituted another type of plasminogen activator such as tissue plasminogen activator (t-PA) of Johannessen et al for the plasminogen activator urokinase of Bode et al in the invention of Bode et al, particularly in light of the teaching of Johannessen et al of the high efficacy and specificity of t-PA and the need for increasing the circulatory half-life of t-PA administered by itself.

For the purpose of examination, claims are given their broadest reasonable interpretation. A peptide mimetic is disclosed in the instant specification on page 12 at lines 7-9 to "include a chemical compound, or an organic molecule or any other peptide mimetic, the structure of which is based on or derived from a binding region of a protein." A definition for the term "grafted" is not disclosed in the instant specification. Instant claim 3 is included because the recitation of a method wherein the claimed product is made carries no patentable weight in these product claims, i.e., as in "and is optimized prior to grafting." Instant claim 19 is included because the said integrins bind to an RGD motif.

Applicant's arguments filed 5/15/00 have been fully considered but they are not persuasive.

Regarding Applicant's comments on page 11 of said amendment at paragraphs 1 and 2, to the disclosed definition of "surface loop" and the comments concerning Barbas et al, the instant claims recite an agent comprising an isolated peptide mimetic which is *based* on an optimized protein surface loop (instant claim 1) or a protein *comprising* an optimized protein surface loop (instant claim 3). Said instant claims 1 and 3 do not recite a limitation wherein the peptide consists of an optimized protein surface loop linked to an agent or a protein. Regarding Applicant's comments on page 12 of said amendment at paragraph 2, the disclosed definition in the instant specification, on page 14 at line 20, of "optimization" includes "affinity maturation." The Smith et al teach affinity maturation.

9. No claim is allowed.

10. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware of in the in the specification.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne DiBrino whose telephone number is (703) 308-0061. The examiner can normally be reached Monday through Friday from 8:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
August 11, 2000

CHRISTINA Y. CHAN
SUPERVISORY PATENT EXAMINER
GROUP 1800/1640